1-(9*H*-Carbazol-4-yloxy)-3-(2-(2-[11C] methoxyphenoxy)ethylamino)-propan-2-ol [11C]Carvedilol

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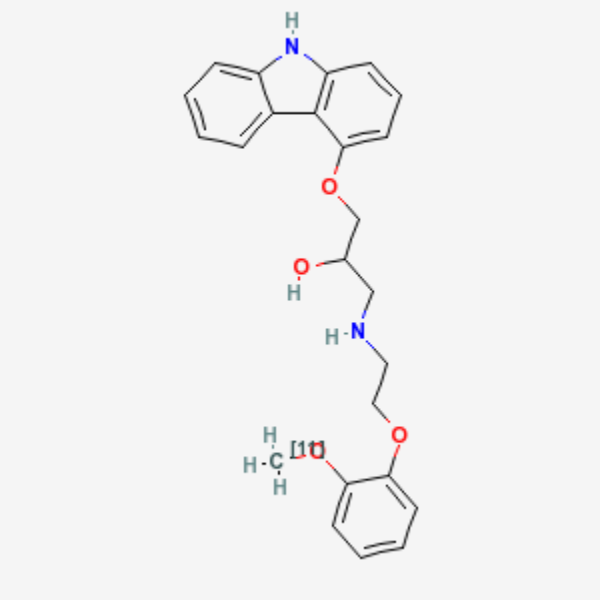
Chemical name: 1-(9*H*-Carbazol-4-yloxy)-3-(2-(2-[11C]methoxyphenoxy) ethylamino)-propan-2-ol
Abbreviated name: [11C]CARV
Synonym: [11C]Carvedilol
Backbone: Compound
Target: P-glycoprotein multidrug transporter, MDR-1
Mechanism: P-glycoprotein substrate
Method of detection: PET
Source of signal: 11C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: No
Human studies: No



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

One of the mechanisms cells use to escape the cytotoxic effects of chemotherapeutic agents, such as Adriamycin, Vinca alkaloids, epipodophyllotoxins, actinomycin D, and Taxol®, is to limit their presence inside the cells through the actions of P-glycoprotein (P-gp), a protein encoded by the multidrug resistance (MDR-1) gene (1, 2). P-gp is an ATP-dependent transmembrane multidrug transporter that is capable of actively pumping a variety of agents out of cells. Overexpression of P-gp in tumor cells (such as renal carcinoma, hepatoma, pheochromocytoma, and colon carcinoma) leads to resistance to anticancer drugs (3). P-gp is also present in a variety of normal cells, such as intestinal mucosal cells, hepatocytes, renal proximal tubule epithelial cells, and endothelial cells of

the blood-brain barrier (4, 5). Calcium channel blockers, cyclosporin A, and its non-immunosuppressive analog PSC 833 are MDR modulators that inhibit transport of P-gp substrates out of cells (6, 7).

Sestamibi (MIBI) is a substrate for P-gp. ^{99m}Tc-MIBI [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.MIBI99mtc] has been approved by the United States Food and Drug Administration as a myocardial perfusion imaging agent for use in single-photon emission computed tomography (SPECT) to assess the risk of future cardiac events. It is also approved as a tumor-imaging agent in breast, lung, thyroid, and brain cancers. 1-(9*H*-Carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]-propan-2-ol (carvedilol), a β-adrenoceptor antagonist, is also a transport substrate for P-gp with a log *P* of 2.0 (8). [^{11}C]Carvedilol ([^{11}C]CARV) was found to be not suitable as a tracer for imaging adrenoceptors in any target organ, such as the brain, heart, lungs, and spleen (9). Brain accumulation of [^{11}C]CARV is reported to be highly sensitive to P-gp modulation by cyclosporin A (10). Therefore, [^{11}C]CARV is being developed as a positron emission tomography (PET) agent to noninvasively study P-gp function.

Synthesis

[PubMed]

In the report by Bart et al. (10), [^{11}C]CARV was synthesized by alkylation of desmethylcarvedilol with [^{11}C]methyltriflate, with subsequent separation by high-performance liquid chromatography. The radiochemical yield was 20-33%, based on [^{11}C]methyltriflate, with a total synthesis time of 55 min. The specific activity was 13-26 TBq/mmol (350-703 Ci/mmol) at the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In a study using the P-gp-negative small cell lung carcinoma GLC_4 and its overexpressing subclone GLC_4/P-gp, cellular accumulation of [^{11}C]CARV was 100% higher in GLC_4 than in GLC_4/P-gp (10). Cyclosporin A (50 μM) increased [^{11}C]CARV accumulation by 2.0-fold ($P = 0.0001$) in GLC_4/P-gp but had no effect in GLC_4. MK571 (50 μM), a multidrug resistance-associated protein (MRP1) inhibitor, had no effect on [^{11}C]CARV accumulation in both cell types.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal rats showed high accumulation of radioactivity, as measured by autoradiography, in the lung, followed by the liver, kidney, and heart at 60 min after injection of [^{11}C]CARV (10). Tracer accumulation in the brain was low. Cyclosporin A (25-50 mg/kg) increased [^{11}C]CARV accumulation in the brain 6 ± 3-fold. This indicates that P-gp-mediated [^{11}C]CARV efflux

can be modulated by cyclosporin A. PET imaging revealed that [11C]CARV accumulated in the brains of rats without or with cyclosporin A treatment (5, 10, 15, 25, and 50 mg/kg). The tracer was rapidly cleared from plasma after injection, with a first phase half-life of 2.3 min and a second, wash-out phase half-life of 108 min. Cyclosporin A had no effects on the plasma kinetics of [11C]CARV. The distribution volume (DV) of [11C]CARV in the brain was 0.3 after injection of 35-50 MBq (0.94-1.35 mCi) of [11C]CARV. At 5 mg/kg cyclosporin A, the DV was increased >1-fold. The maximum increase in DV was 2-fold after 15 mg/kg cyclosporin A with no further increases at higher dosages of cyclosporin A. Metabolism studies using [14C]CARV in rats, mice, and dogs showed that all metabolites are more hydrophilic than the parent compound and are expected to have negligible brain uptake (11).

Other Non-Primate Mammals

[PubMed]

No relevant publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No relevant publications are currently available.

References

1. Endicott JA, Ling V. The biochemistry of P-glycoprotein-mediated multidrug resistance. Annu Rev Biochem 58:137–171; 1989. (PubMed)
2. Gottesman MM, Pastan I. Biochemistry of multidrug resistance mediated by the multidrug transporter. Annu Rev Biochem 62:385–427; 1993. (PubMed)
3. Fojo AT, Ueda K, Slamon DJ, Poplack DG, Gottesman MM, Pastan I. Expression of a multidrug-resistance gene in human tumors and tissues. Proc Natl Acad Sci U S A 84(1):265–269; 1987. (PubMed)
4. Piwnica-Worms D, Rao VV, Kronauge JF, Croop JM. Characterization of multidrug resistance P-glycoprotein transport function with an organotechnetium cation. Biochemistry 34(38):12210–12220; 1995. (PubMed)
5. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. Proc Natl Acad Sci U S A 84 (21):7735–7738; 1987. (PubMed)
6. Hughes CS, Vaden SL, Manaugh CA, Price GS, Hudson LC. Modulation of doxorubicin concentration by cyclosporin A in brain and testicular barrier tissues expressing P-glycoprotein in rats. J Neurooncol 37(1): 45–54; 1998. (PubMed)
7. Mayer U, Wagenaar E, Dorobek B, Beijnen JH, Borst P, Schinkel AH. Full blockade of intestinal P-glycoprotein and extensive inhibition of blood-brain barrier P-glycoprotein by oral treatment of mice with PSC833. J Clin Invest 100(10):2430–2436; 1997. (PubMed)

8. Jonsson O, Behnam-Motlagh P, Persson M, Henriksson R, Grankvist K. Increase in doxorubicin cytotoxicity by carvedilol inhibition of P-glycoprotein activity. Biochem Pharmacol 58(11):1801–1806; 1999. (PubMed)
9. Doze P, Elsinga PH, Maas B, Van Waarde A, Wegman T, Vaalburg W. Synthesis and evaluation of radiolabeled antagonists for imaging of beta-adrenoceptors in the brain with PET. Neurochem Int 40(2): 145–155; 2002. (PubMed)
10. Bart J, Dijkers EC, Wegman TD, de Vries EG, van der Graaf WT, Groen HJ, Vaalburg W, Willemsen AT, Hendrikse NH. New positron emission tomography tracer [(11)C]carvedilol reveals P-glycoprotein modulation kinetics. Br J Pharmacol 145(8):1045–1051; 2005. (PubMed)
11. Schaefer WH, Politowski J, Hwang B, Dixon F, Goalwin A, Gutzait L, Anderson K, DeBrosse C, Bean M, Rhodes GR. Metabolism of carvedilol in dogs, rats, and mice. Drug Metab Dispos 26(10):958–969; 1998. (PubMed)